Webinars
Constitutional thrombocytopenia
EuroBloodNet

MYH9-Related Disease

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ERN-EuroBloodNet Topic on Focus: Constitutional thrombocytopenia

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Conflicts of interest

	María L Lozano	José Rivera
Research support/PI	Amgen	Zacros
Employee	-	-
Consultant / Honoraria	Amgen, Argenx, Grifols, Novartis, Sobi, UCB	-
Major stockholder	-	-
Speaker's fees	Amgen, Grifols, Novartis, Sobi	Terumo Bct
Scientific advisory board	Amgen, Argenx, Grifols, Novartis, Sobi, UCB	-

Learning objectives of the webinar

Part 1-JR

1. MYH9-RD: Definition, general features, prevalence
2. Diagnosis
3. MYH9 gene and protein, function and regulation
4. MYH9 molecular pathology: Genotype-phenotype relationship
5. Pathogenic molecular mechanisms of MYH9-RD underlying hematological and extra-hematological manifestations

Part 2-ML

6. Clinical picture of MYH9-RD & potential role of MYH9 variants in other diseases
7. Clinical management and treatment of MYH9-RD

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MYH9-RD: Definition, general features, prevalence

1. **Autosomal-dominant thrombocytopenia caused by monoallelic genetic variants in *MYH9***, the gen encoding for the heavy chain of Non-muscle myosin IIA (NMHC-IIA)

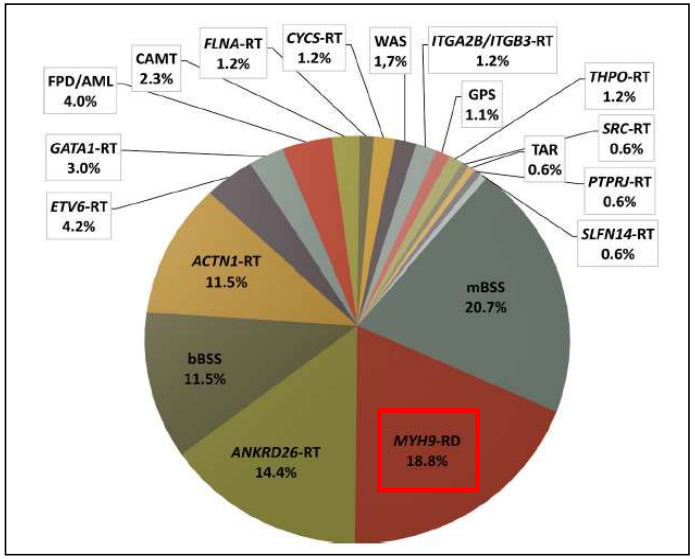
2. **MYH9-RD includes a spectrum of syndromes**, previously classified as distinct diseases: May-Hegglin, Sebastian, Fechtner and Epstein syndromes, and autosomal dominant deafness DFNA17

3. **The hallmark features of MYH9-RD are**
   Thrombocytopenia: mild to severe and stable throughout life ;
   Market **platelet macrocytosis** with giant platelet
   Inclusions of NMHC-IIA in the cytoplasm of **granulocytes**:
   basophilic Döhle-like bodies on conventional blood smears examination (40-80% of cases)
   NMHC-IIA agreggates by IF staining of BS (100%)
   Mild bleeding tendency (influenced by platelet count)(≈normal platelet function)

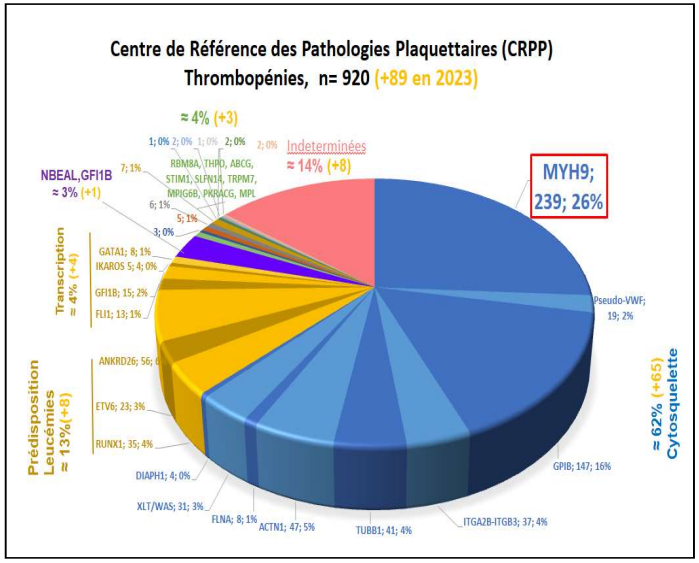
4. **Most MYH9-RD patients develop extra-hematological features**:
   Sensorineural deafness
   Kidney disease
   Presenile cataracts
   Elevation of liver enzymes (benign)

MYH9-RD: Prevalence

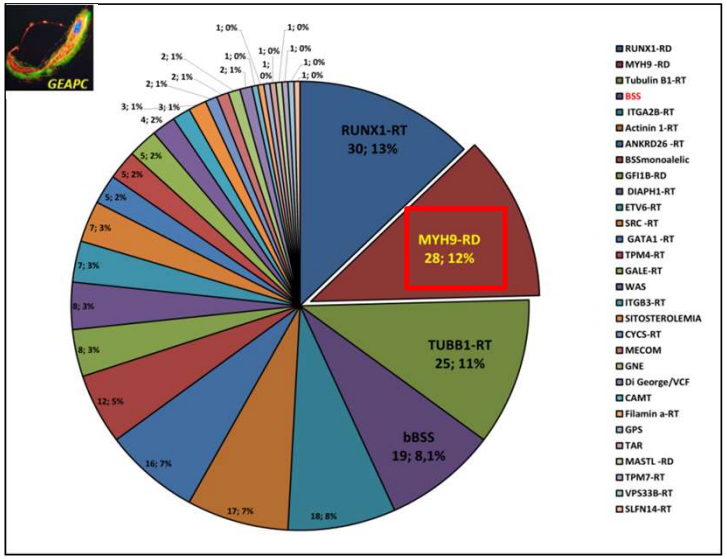
MYH9-RD is considered the most frequent form of IT worldwide (≈ 25%) (ANKRD26-RT, mBSS & ACTN1-RT)



ITs forms in the Italian series of 335 consecutive families with IT. mBSS is the most frequent due a founder effect of c.515C>T in GP1BA. Pecci & Balduini , Blood Review, 2021
250 MYH9-RD case in the Italian registry (A Pecci data)



ITs forms in France
Kindly provided by MC Alessi



MYH9-RD, is 2º most frequent IT in the Spanish GEAPC series: 306 Patients (184families) with suspicion of IT
IT genetic diagnosis in 236 (77,1%) , 145 pedigree;
30 forms of IT (≈23% UIT) (unpublished data)

- ✓ No prevalence variations across ethnic populations
- ✓ 3-5: 1,000,000…….likely underestimated
- ✓ 40: 1,000,000……. according to the frequency MYH9 genetic variants in GenomAD database, (Fernandez-Perez et al. Clinical Kidney Journal, 2019, 488–493)

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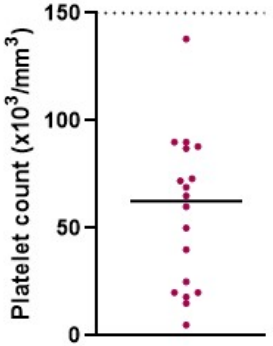
MYH9-RD: Diagnosis

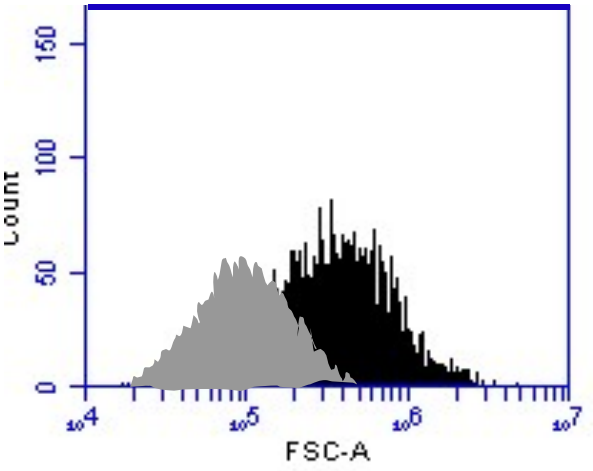
- ✓ **Clinical assessment: Lifelong thrombocytopenia, absence of acquired causes, family history, bleeding, associated extra-hematological features (kidney alteration, deafness, cataracts) (age dependent)**
- ✓ **Laboratory diagnosis**

Automatic full blood cell count



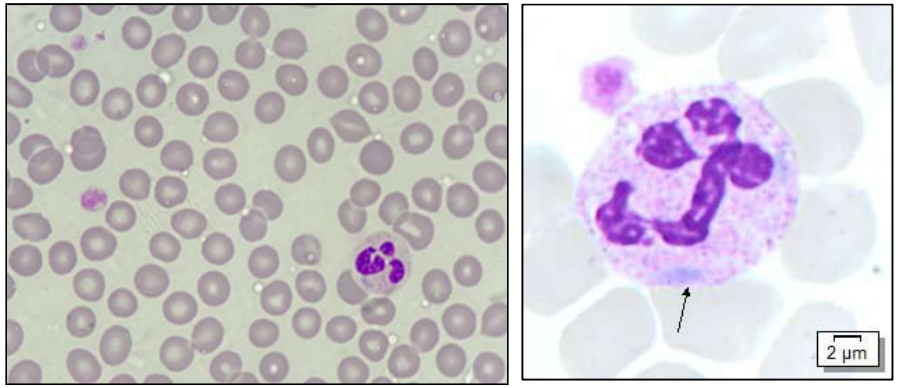
Automated counter fail in detecting platelet macrocytosis.
Platelet count in 19 MYH9-RD cases

Flow cytometry assessment



CASE 19-019: MYH9 c.5521G>A [p.Glu1841Lys]
Automated Pl count: 6000/uL; FC count: 24000/ul
Median FSC-A: 328,301
(normal range: 81.915 ± 25422)

Blood smear examination



Case 19:
Giant platelet (>50%)
Döhle-like bodies in neuthrophils.
Reported to be recognized in in 42-84%
(Seri et. All 2003; Balduini et al 2011)

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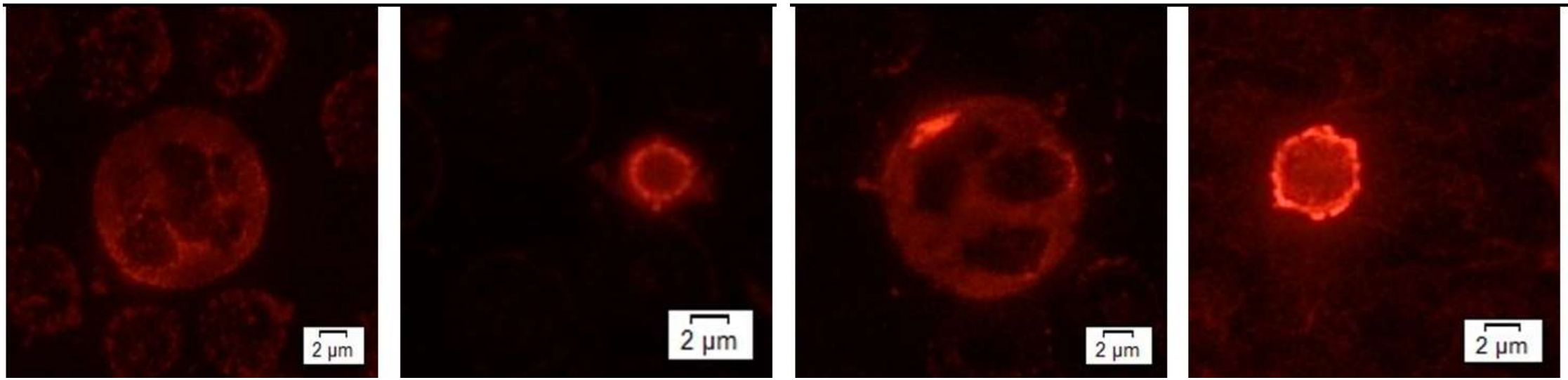
MYH9-RD: Laboratory Diagnosis IF

Blood smear MYH9 immunostaining

Control | **MYH9-RD, case 19-019**



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Kunishima et al., 2003; Savoia et al., 2010;
Kitamura et al., 2013; Greinacher et al., 2017

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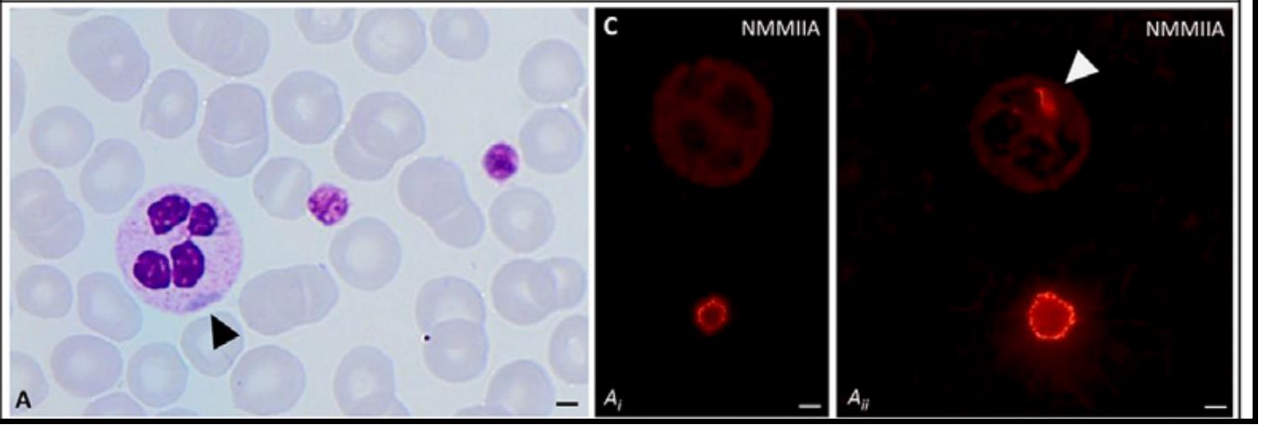
MYH9-RD: Laboratory Diagnosis IF

Validation of immunofluorescence analysis of blood smears in patients with inherited platelet disorders.

IPD Pathogenic mutations	Previously reported pattern	Changes found in patients	Images
MYH9-RD p. Glu1505Lys § p.Glu1841Lys § p.Ser96Leu §	Platelet macrocytosis with giant platelets; Döhle-like inclusion bodies in the leukocytes; diffused distribution of NMMIIA in platelets	**5/5** (3 pedigrees)	

Blood smear MYH9 immunostaining

Zaninetti C, Leinøe E, Lozano ML, Rossing M, Bastida JM, Zetterberg E, Rivera J, Greinacher A. J Thromb Haemost. 2023 Apr;21(4):1010-1019. PMID: 36732160.

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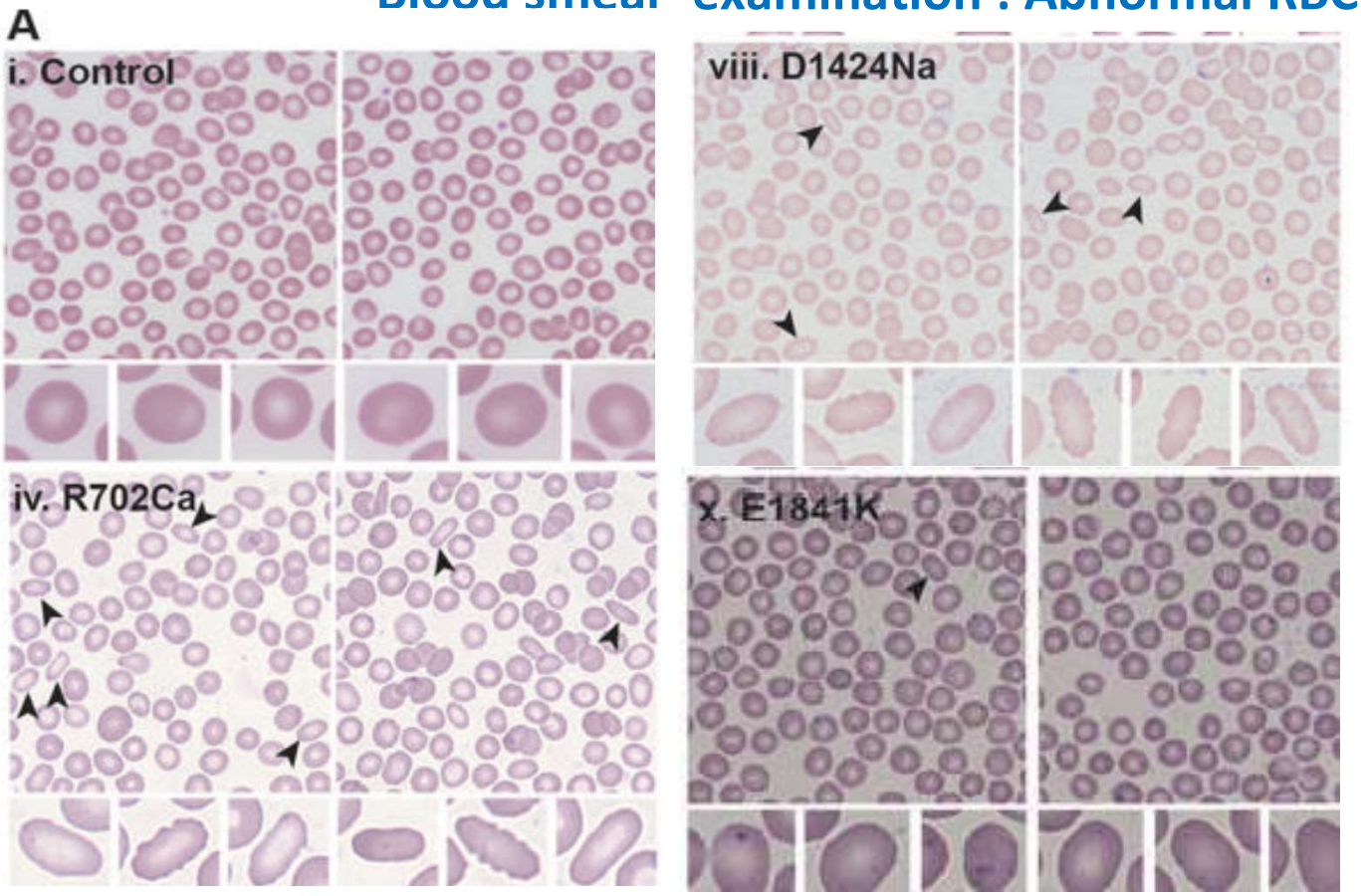
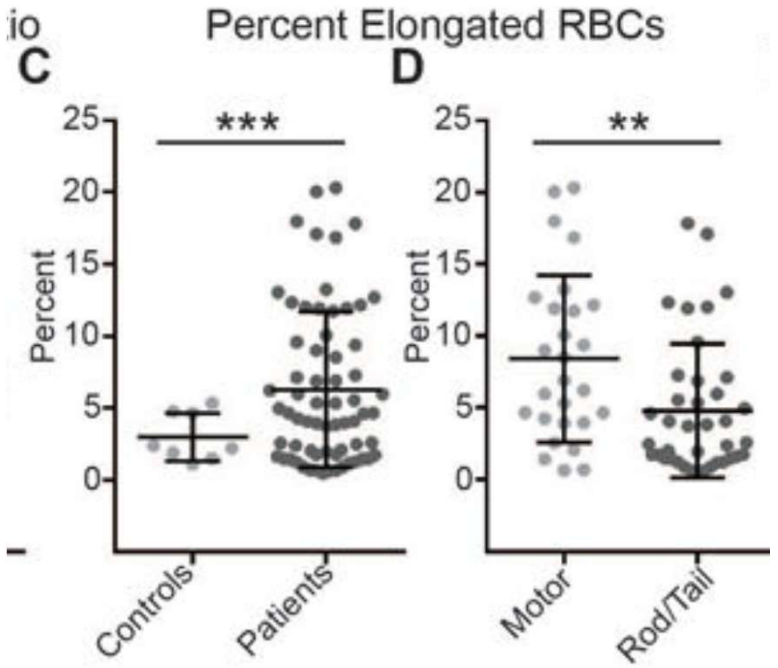
MYH9-RD: Laboratory Diagnosis IF

Blood smear examination : Abnormal RBC morphology





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Smith AS, et al. MYH9-related disease mutations cause abnormal red blood cell morphology through increased myosin-actin binding at the membrane. Am J Hematol. 2019 . PMID: 30916803.

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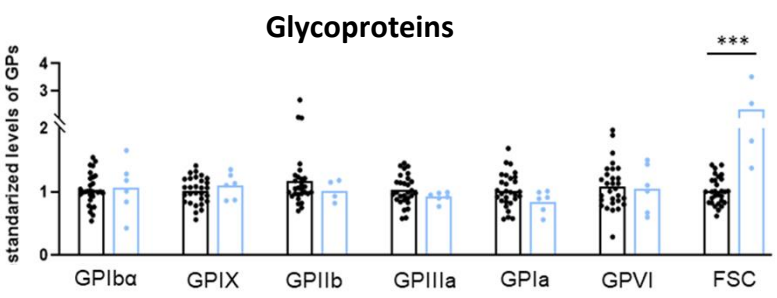
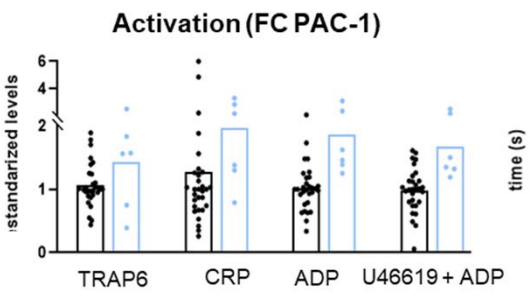
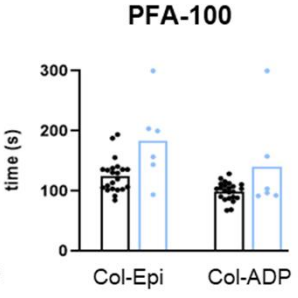
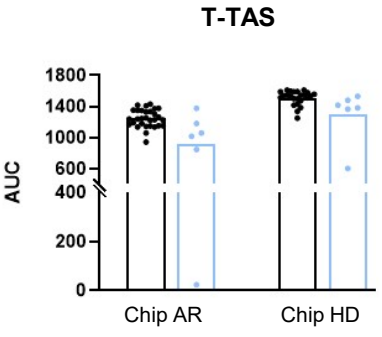
MYH9-RD: Diagnosis

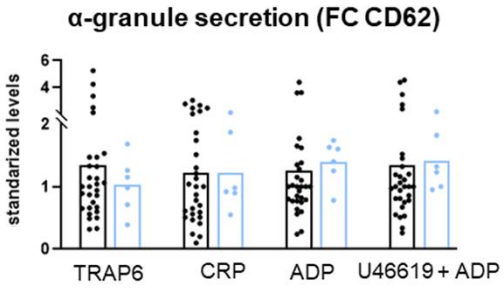
✓ Platelet function testing is of limited value in MYH9-RD diagnosis

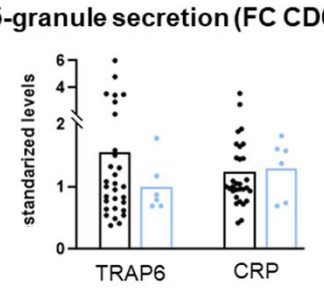


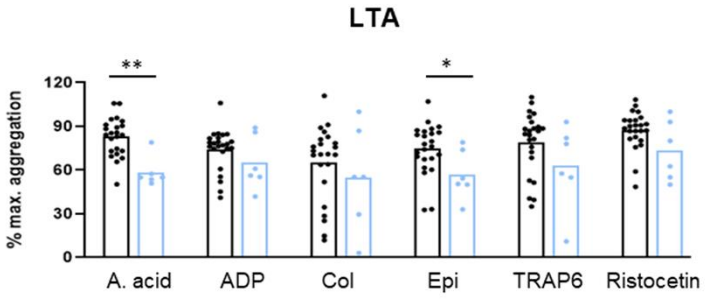


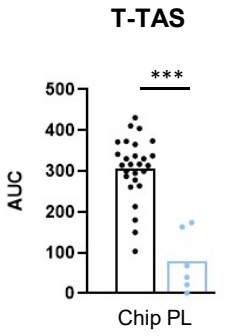












☐ Healthy subjects, n=30 ☐ MYH9-RD patients, n=6

Platelet function testing using different methods (unpublished)

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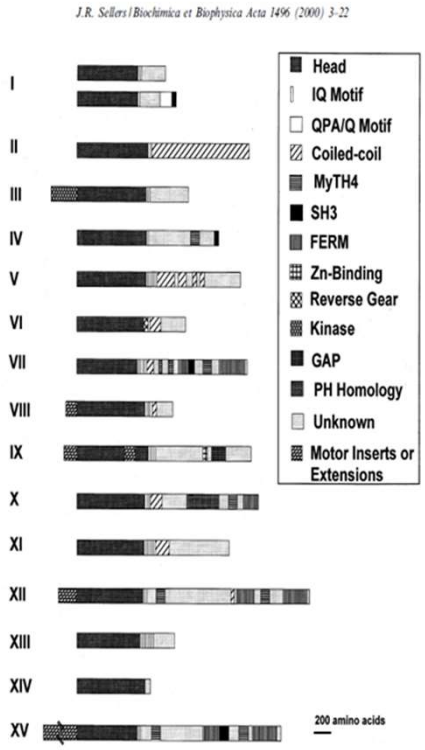
Myosins/Myosin II/ Non-muscle Myosin II

Myosins: Large superfamily of proteins that use energy from ATP hydrolysis into a conformational change that propels molecular motion.



15 classes

Myosin class II (or conventional myosins)→the only known for decades.
Class II myosins form filaments and create force and tension, because their motor domain binds to actin filaments.

Class II myosins are :

Muscle myosin II (MM II): skeletal and cardiac and smooth muscle….. Muscle contraction
Non-muscle myosin II … cell contractility, morphology, cytokinesis and migration

- NM IIA… MHCII-A----- *MYH9* gene.
- NM IIB… MHCII-B----- *MYH10* gene
- NM IIC… MHCII-C----- *MYH14* gene

Considerable homology and some overlapping functions→ Evolved from duplication of an ancestral gen

Differences in enzymatic properties, subcellular localization, molecular interaction and tissue distribution.

MHCII-A is the only present in platelets and most blood cells.
Immature Mks express NM IIB (MYH10), which is dowregulated with maduration

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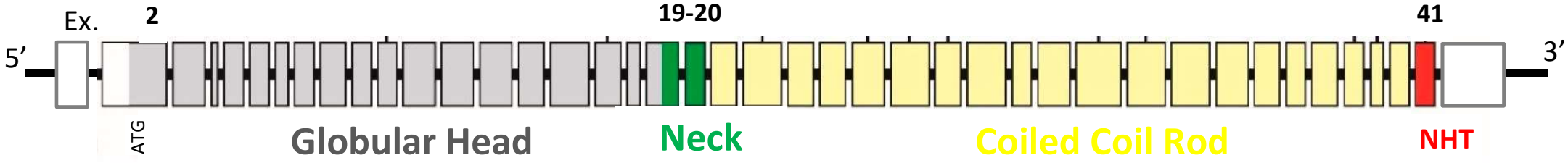
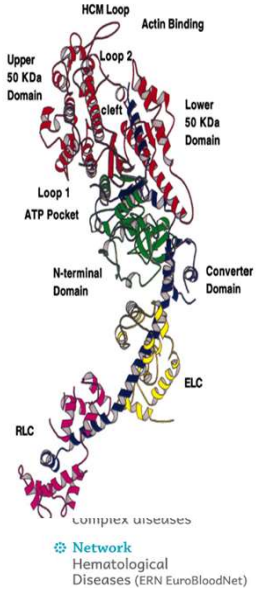
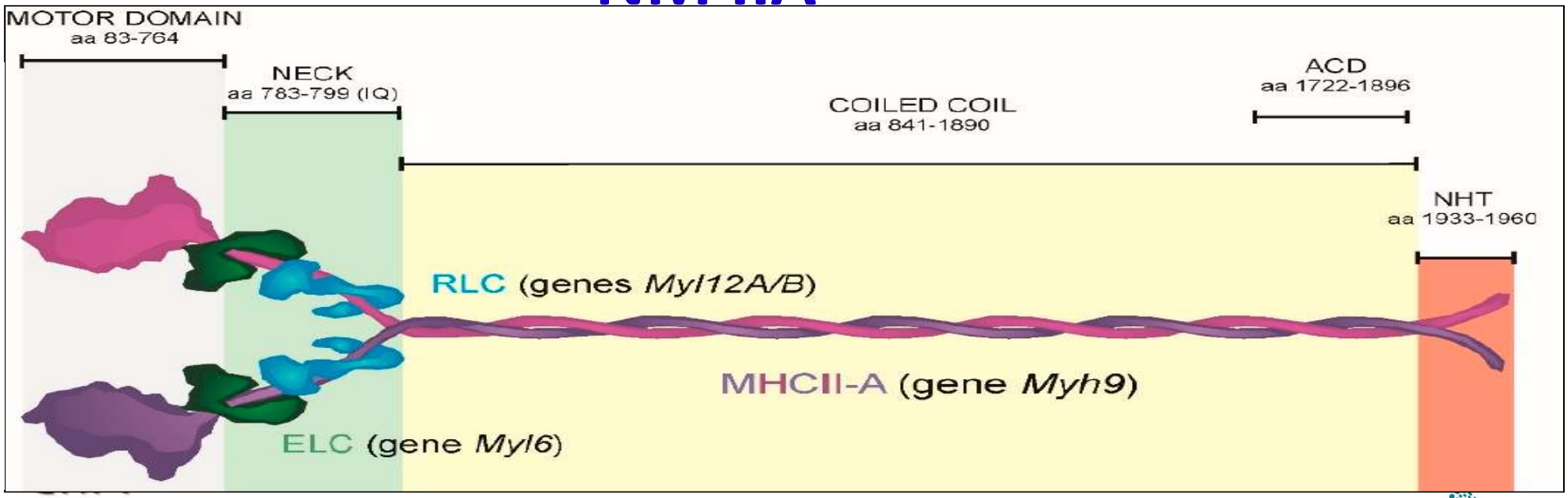
MYH9 gene and NM IIA protein



MYH9: Chromosome 22q12.3, 106 kbp; 41 exons; a well-conserved gene through evolution (mouse ortholog [Myh9] is 97% similar; open reading frame Ex 2-41; protein 1960 aa (NMHC IIA)

NM IIA





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Asensio-Juarez et al. Cells, 2020; Pecci et al. Gene 2018

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NM II A protein play key functions

- ✓ **Class II non-muscle myosins [NM II (A/B/C)] participate in processes requiring force production and translocation of the actin cytoskeleton** (cytokinesis, cell migration, polarization, adhesion, maintenance of cell shape, and signal transduction)

- ✓ **NM IIA is present** in a large variety of cells **during early embryonic development** (80% of total NMII)
  - Key role in formation of functional visceral endoderm (Non requiring full motor activity; replaced by NM II B/C)
  - Critical in (mouse) placenta formation (requiring full motor activity; Not replaced by NM II B/C)

- ✓ **NM IIA**, vs. B/C isoforms, **show the highest actin-activated MgATPase activity and rate of sliding actin filaments** (in vitro motility), but much lower than Muscle Myosisn II. Thus, NMII-A is well designed for quick processes that require small-scale forces and dynamic filament assembly and disassembly, for example in migrating cells.

- ✓ Some cells and tissues express different NM II (A/B/C) isoforms in variable amounts. **NM IIA is the most widely distributed**. The spleen, platelets and most blood cells contain only NM IIA

- ✓ **NM II A/B/C isoforms**, if co-present, **can co-assemble intracellularly into heterotypic filaments**, and be performing both isoform-specific and isoform redundant functions

Regulation of NM IIA activity

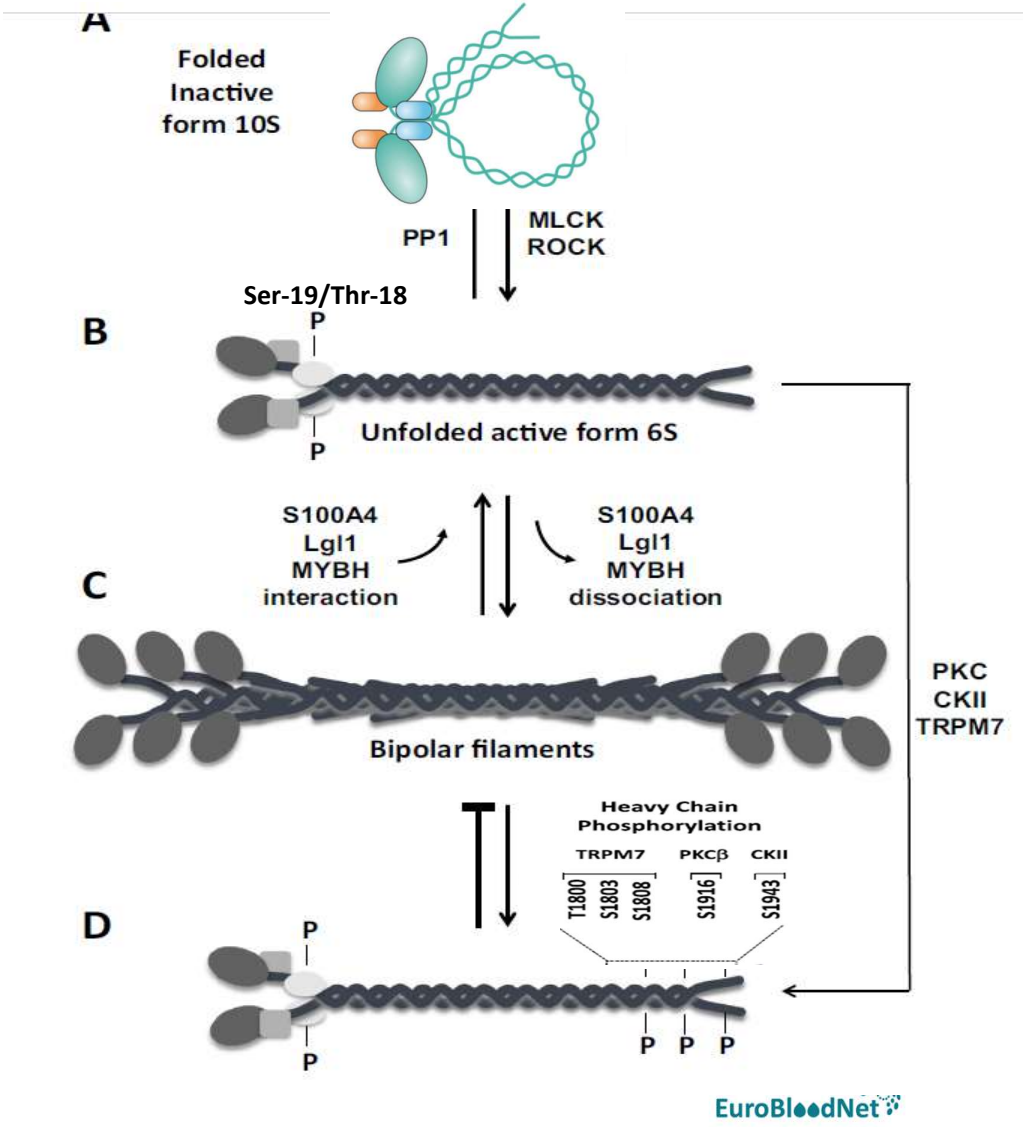
1) Conformational switch upon RCL phosphorylation

RLC Ser-19/Thr-18 phosphorylation by MLCK/ROCK & dephosphorylation by PP1

- Transition 10S→6S allows bipolar filament formation, increasing actin –activated Mg ATPase & sliding of actin filaments by myosin
- The 6S form is highly unstable→ Need to increases its stability by forming electrostatic bonds with other 6S forms, or it rapidly folds back into the more stable 10S form.

2) NMHC IIA phosphorylation and it interaction wit other proteins

- Phosphorylation of NMHC IIA C-terminal end by PKCB, CKII & TRPM7 kinases→ Prevent bipolar filament formation and dissociate the myosin filaments by adding the negatively charged phosphate group or to prevent filament formation
- Interaction with other proteins, S100A4, Lgl1 & MYBH→ prevent filament formation and favour disassembly of formed filaments



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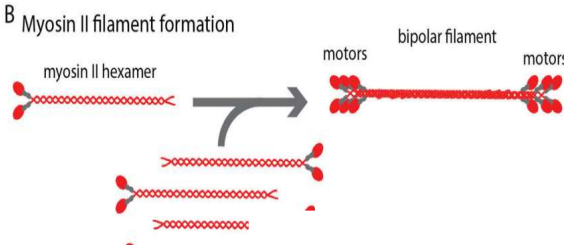
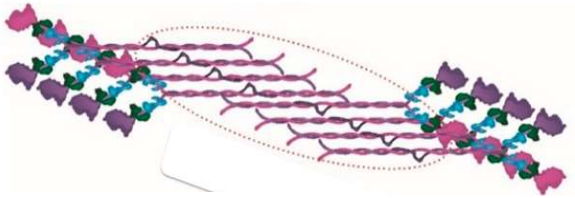
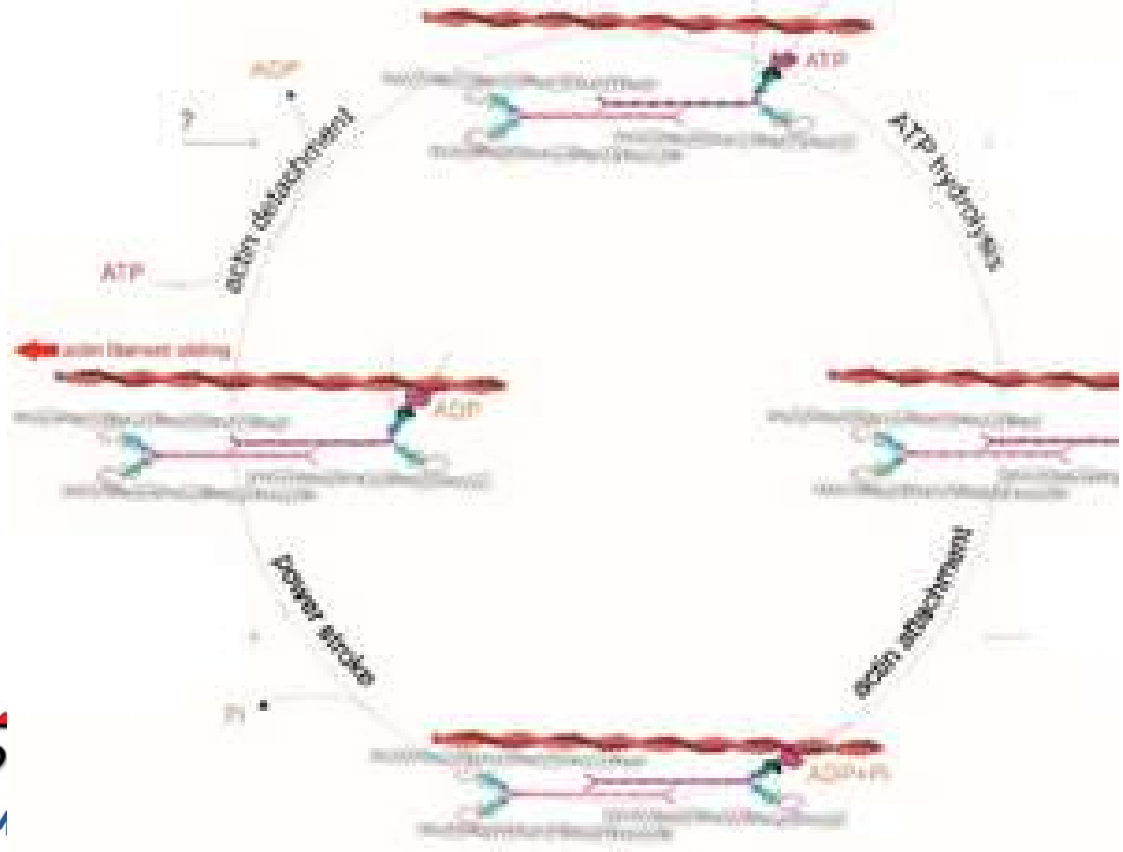
Pecci et al. Gene 2018; Asensio-Juarez et al. Cells, 2020; Vicente –Manzanares Nat Rev Mol Cell Biol. 2009

NM II A filament assembly





mini-filaments;
20–30 NM IIA hexamers
each ≅300 nm



The cross-swinging cycle

Fenix & Burnette. Cyoskeleton, 2018
Asensio-Juarez et al. Cells, 2018

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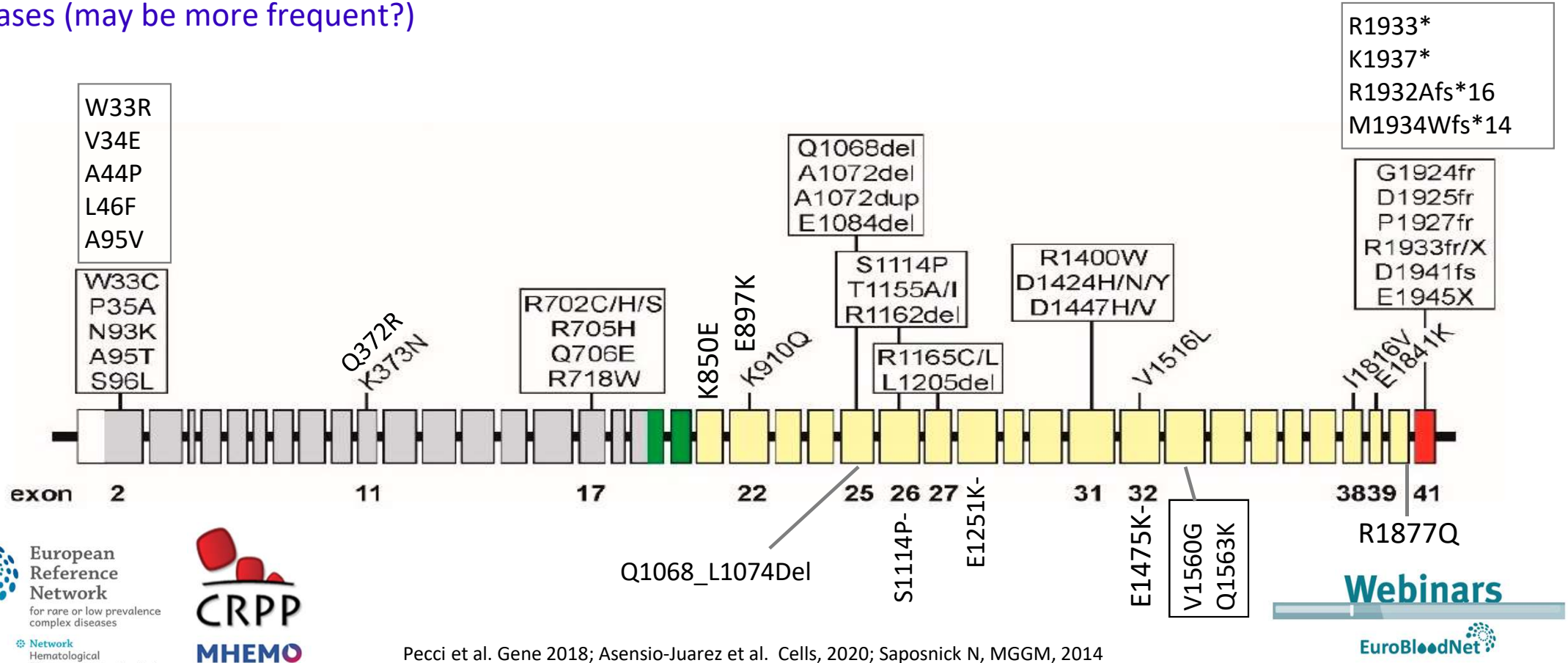
MYH9 molecular pathology causing MYH9-RD

About 100 different heterozygous mutations

Most are missense variants affecting 12 exons (head & coiled coil domains)

Nonsense, splicing, duplications and in-frame deletions are rare (<25% of the patients): NHT or nearby

25-35% are de Novo variants. Somatic or germinal mosaicism has been rarely reported to explain sporadic cases (may be more frequent?)



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Pecci et al. Gene 2018; Asensio-Juarez et al. Cells, 2020; Saposnick N, MGGM, 2014

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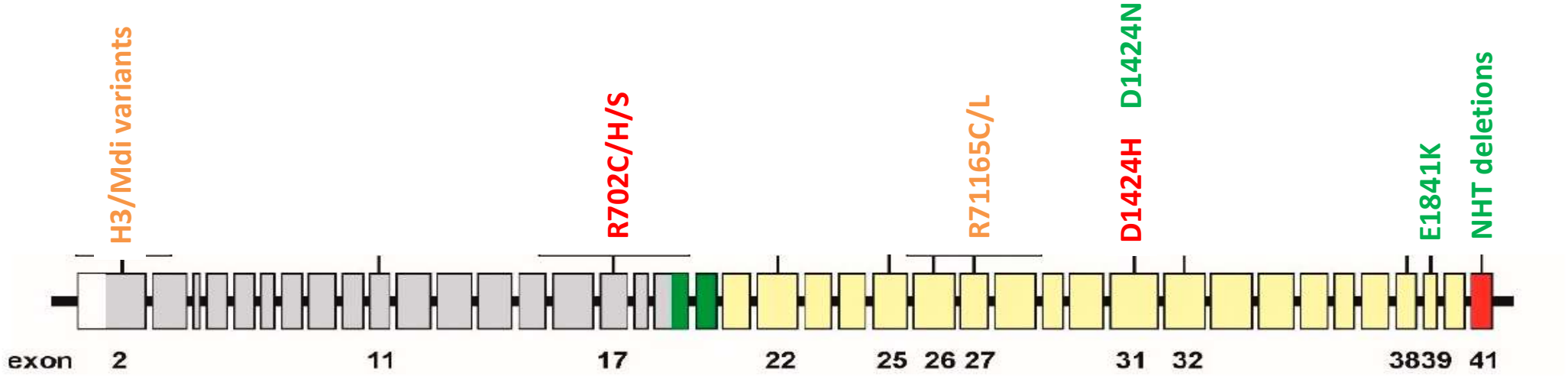
MYH9-RD: Genotype-Phenotype relationship

- ✓ The platelet phenotype and the risk of developing late-onset manifestations of MYH9-RD and their severity are dependent on the specific MYH9 mutation:
- ✓ In general Head domain variants >>>severe>>> Tail domain variants
  (≈30 x109 pl/L vs. ≈80 x109 pl/L ; increased NM IIA aggregates on IF staining)

Pecci et al., Human Mutation 2014

- ✓ 255 consecutive patients
- ✓ 7 MYH9 genotypes account for about 85% of disease cases



High risk /Moderate risk/ Low risk

MYH9-RD: Genotype-Phenotype relationship

Table 6. Summary of the Risk of Occurrence of Extra-Hematological Manifestations of *MYH9*-RD According to Seven *MYH9* Genotypes

	Nephropathy	Deafness	Cataracts
SH3/MD interface substitutions	Low risk	Before age 60 years in all patients	Low risk
R702 substitutions	Before age 40 years in all patients Progression to ESRD in all patients	Before age 40 years in all patients	Low risk
R1165 substitutions	Low risk	Before age 60 years in all patients	Low risk
p.D1424H	High risk Progression to ESRD in a minority of patients	Before age 60 years in all patients	Probably higher risk
p.D1424N	Very low risk	Low risk	Low risk
p.E1841K	Low risk	Low risk	Low risk
NHT deletions	Very low risk	Low risk	Very low risk

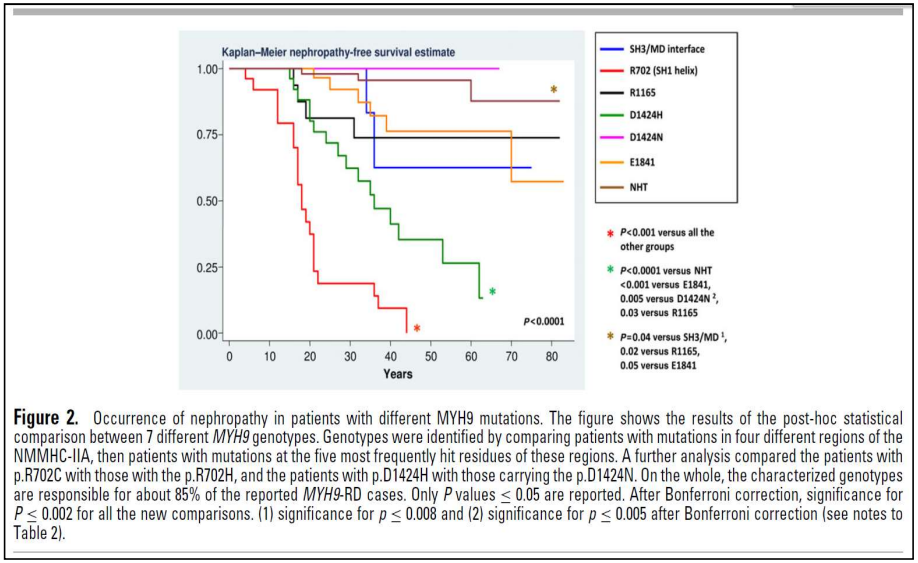


Figure 2. Occurrence of nephropathy in patients with different MYH9 mutations. The figure shows the results of the post-hoc statistical comparison between 7 different *MYH9* genotypes. Genotypes were identified by comparing patients with mutations in four different regions of the NMMHC-IIA, then patients with mutations at the five most frequently hit residues of these regions. A further analysis compared the patients with p.R702C with those with the p.R702H, and the patients with p.D1424H with those carrying the p.D1424N. On the whole, the characterized genotypes are responsible for about 85% of the reported *MYH9*-RD cases. Only *P* values $\leq$ 0.05 are reported. After Bonferroni correction, significance for $P \leq 0.002$ for all the new comparisons. (1) significance for $p \leq 0.008$ and (2) significance for $p \leq 0.005$ after Bonferroni correction (see notes to Table 2).

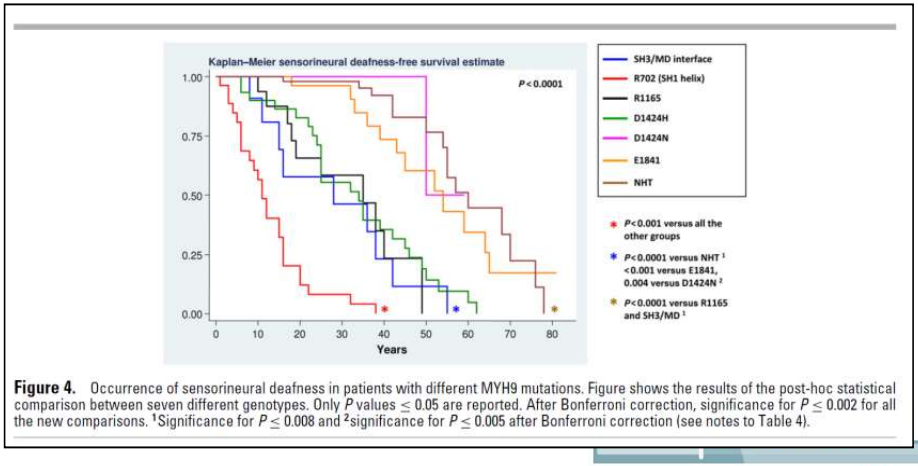


Figure 4. Occurrence of sensorineural deafness in patients with different MYH9 mutations. Figure shows the results of the post-hoc statistical comparison between seven different genotypes. Only *P* values $\leq$ 0.05 are reported. After Bonferroni correction, significance for $P \leq 0.002$ for all the new comparisons. [1]Significance for $P \leq 0.008$ and [2]significance for $P \leq 0.005$ after Bonferroni correction (see notes to Table 4).

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Pecci et al. Human Mutation 2014

Sposnick N, MGGM, 2014

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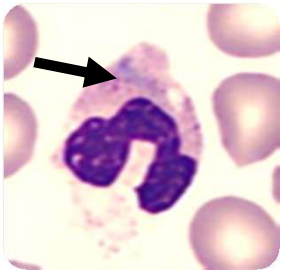
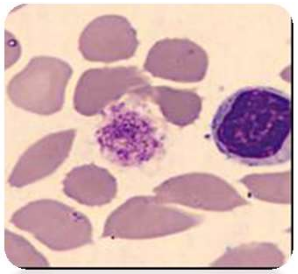
Exceptions for reported Genotype-Phenotype risk assessment cab be found

Case ITP with deafness and end-stage renal disease





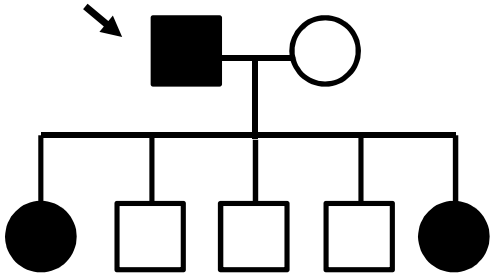
42-year-old patient with thrombocytopenia (37x10^9/l; MPV 14 fl)

Diagnosis of ITP. Corticoids and splenectomy

Bilateral hearing loss

End-stage renal disease.
Underwent renal transplantation at 36 years of age

Died from COVID

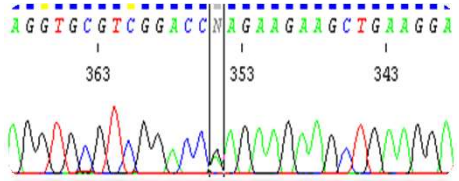


22 years old.
Plt 66x10^9/L. ↑MPV
Proteinuria

11 years old.
Plt 58x10^9/L. ↑ MPV

MYH9

c.5521G>A p.E1841K



Identifying a theoretical low risk-mutation, should not preclude a close medical follow-up of the patients with MYH9-RD

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Molecular mechanisms underlying hematological and extra-hematological manifestations of MYH9-RD and genotype-phenotype correlation

MYH9-RD is highly heterogeneous in terms of clinical manifestations and severity.

Why is that?
What are the underlying molecular mechanism of these clinical manifestations ?
Why is there such an strong genotype-phenotype relationship?

The MYH9-RD represent a very complex system contributed by:

- ✓ nature of the mutations
- ✓ the amount of protein produced and its functional degree
- ✓ The tendency of the mutant protein to aggregate
- ✓ the role or participation of other MHC II isoforms (B/C) or other proteins

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Asensio-Juarez et al. Cells, 2020

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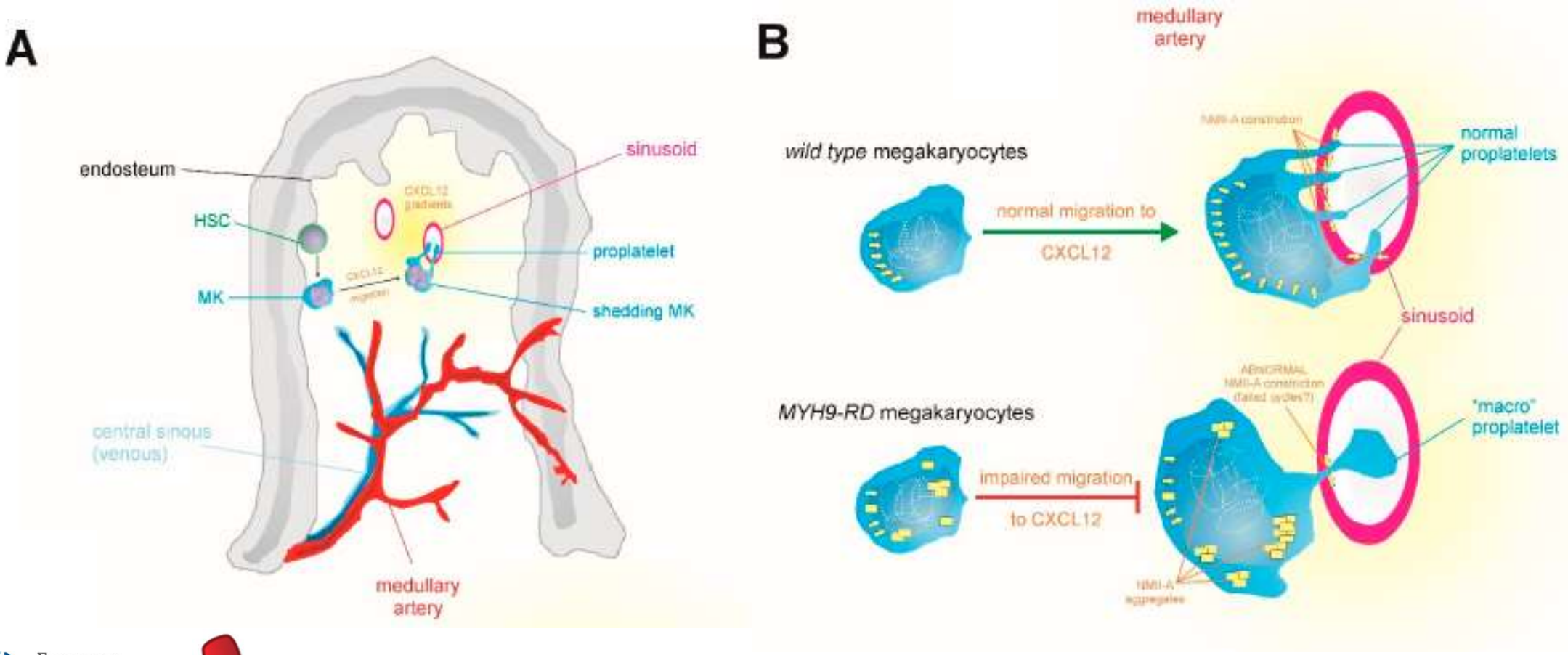
Pathogenesis of macrothrombocytopenia in MYH9-RD



Asensio-Juarez et al. Cells, 2020

Pathogenic molecular mechanisms of MYH9-RD underlying extra-hematological manifestations

- ✓ **Remains poorly understood**
- ✓ **Genetic alterations are, again , expected to greatly influence the development and evolutions of the late onset manifestation of MYH9-RD patients**
  - Different mutations cause diverse molecular effects (ATPase activity/constriction capacity; conformational change dynamics and dimerization, oligomerization into filaments, actin interaction)
  - Different mutations cause various degrees of protein aggregation over time
  - NMII-A, either wild-type or mutant, can copolymerize with other myosins or other proteins.

- ✓ **Nephropathy:** *MYH9* mutations cause podocyte injury resulting in proteinuria & progressive glomeruloesclerosis (podocyte damage seen in MYH9-RD mice models & in kidney biopsies of MYH9-RD patients). Aggregates of NM IIA may contribute to this renal damage

- ✓ **Hearing Loss:** *MYH9* mutations also cause deafness by disrupting the structural integrity of stereocilia in hair cells of the organ of Corti

- ✓ **Cataract:** Maybe favoured by aggregates of non-functional mutant NM IIA in the epithelial cells of the crystalline

Learning objectives of the webinar

Part 1-JR

1. MYH9-RD: Definition, general features, prevalence
2. Diagnosis
3. MYH9 gene and protein, function and regulation
4. MYH9 molecular pathology: Genotype-phenotype relationship
5. Pathogenic molecular mechanisms of MYH9-RD underlying hematological and extra-hematological manifestations

Part 2-ML

6. **Clinical picture of MYH9-RD & potential role of MYH9 variants in other diseases**
7. **Clinical management and treatment of MYH9-RD**

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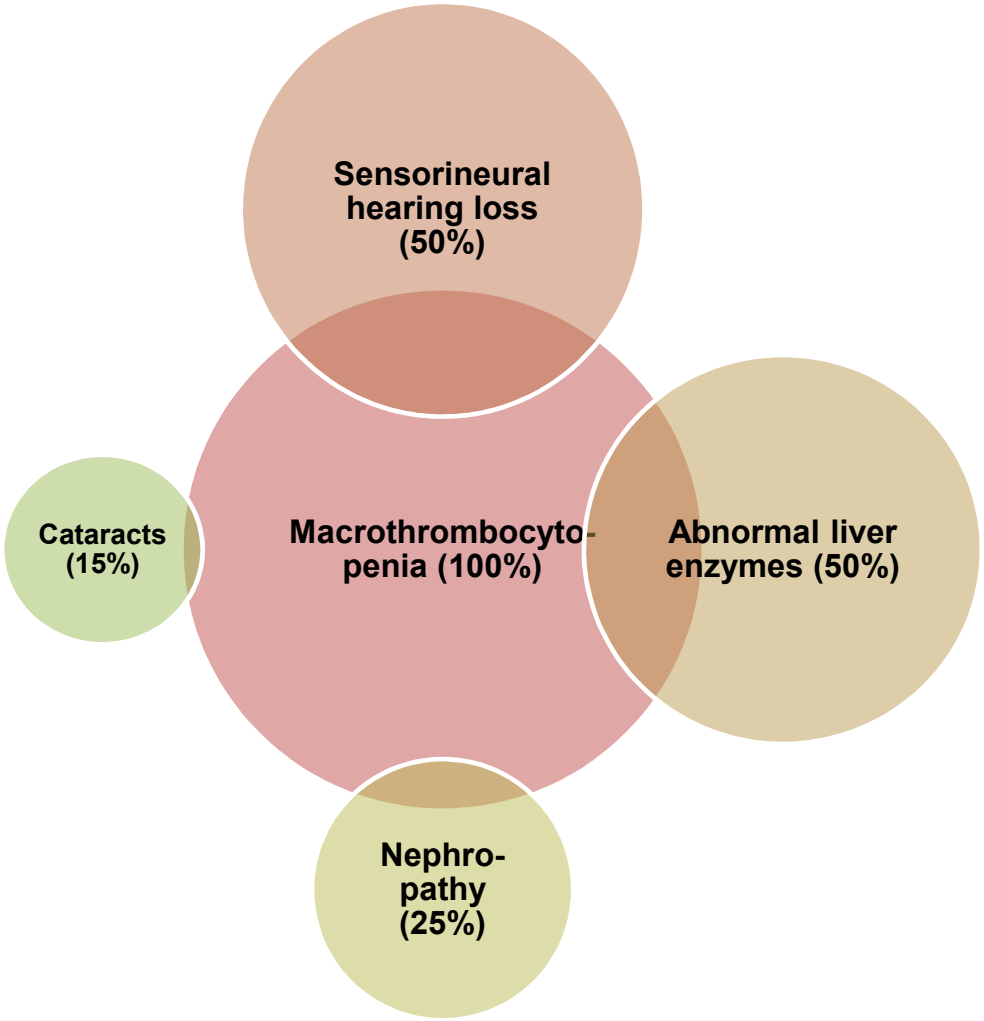
MYH9-Related Disease: Frequency of Select Features



Savoia A, Pecci A. MYH9-Related Disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2689/

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MYH9-Related Disease:Macrothrombocytopenia and bleeding tendency

Macrothrombocytopenia (98% of patients)	General Characteristics	Present from birth
		Only 2% of patients have platelet counts within normal range
	Evaluation	Electronic counters may understimate platelet counts (use microscopic evaluation and/or flow cytometry)
Bleeding tendency (80-90% of patients)	General characteristics	~30% of patients have spontaneous bleeding; in the majority increased bleeding is present only after hemostatic challenges.
	Evaluation	Use of standardized questionnaires (e.g., ISTH Bleeding Assessment Tool) are recommended.
Differential diagnosis	Acquired thrombocytopenia: Mostly immune thrombocytopenia	
	Inherited thrombocytopenia: Bernard Soulier syndrome	

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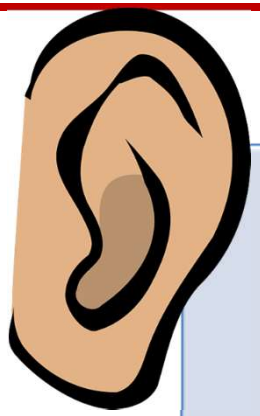
MYH9-Related Disease: Sensorineural hearing loss



General characteristics (50% of patients)

- Observed in about 50% of individuals at a mean age of 33 years
- An increase in 15% of individuals evenly occurs from the first to the sixth decade of life, with earlier onset hearing loss progressing more rapidly and resulting in severe-to-profound deafness

Evaluation

- Audiogram (speech recognition tests in case of severe deafness)

MYH9-Related Disease: Nephropathy

General characteristics (25% of patients)

- Glomerular nephropathy in MYH9-RD presents with proteinuria and microhematuria.
- Mean age of onset is 27 years
- Kidney damage is often progressive, leading to end-stage renal disease in most cases

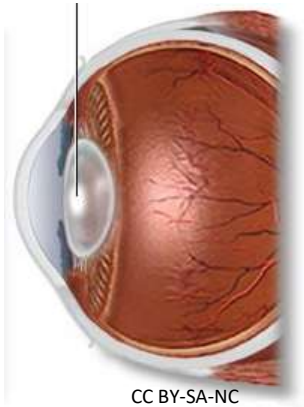
Evaluation

- Urinalysis, 24-hour protein, or protein (or albumin) to creatinine ratio on a spot urine sample; serum concentration of creatinine

Differential diagnoses for oto-renal syndromes

Clinical syndrome	Ear	Kidney	Gene
Alport syndrome	Sensorineural hearing loss	Hematuria; kidney failure; ultrastructural changes of the glomerular basement membrane	*COL4A3, COL4A4, COL4A5*
Alström syndrome	Sensorineural and conductive hearing loss	Glomerulosclerosis, tubular atrophy and interstitial fibrosis; nephrocalcinosis; recurrent urinary tract infections; urethral dysnergia	*ALMS1*
Autosomal recessive distal renal tubular acidosis	Sensorineural hearing loss	Hypokalaemic hyperchloraemic metabolic acidosis	*ATP6V1B1, ATP6V0A4*
Bartter syndrome type 4A (or 4B)	Sensorineural hearing loss	Diabetes insipidus; renal salt wasting; kidney failure	*BSND* (both *CLCNKA* and *CL CNKB*)
Branchio-oto-renal (BOR) syndrome	Hearing loss; preauricular pits; auricular malformations; atresia to stenosis of the external auditory canal; underdeveloped cochlea and semicircular canals	Duplications of collecting system; renal hypoplasia; cystic dysplasia and agenesis; hydronephrosis; ureteropelvic junction obstruction; vesicoureteral reflux; basement membrane splitting and mesangial proliferation	*EYA1, SIX5, SIX1*
Fabry disease	Hearing loss	Glycolipid deposits in glomerular, tubular epithelial and vascular cells; segmental and global glomerulosclerosis; tubular atrophy and interstitial fibrosis; kidney failure	*GLA*
Hypoparathyroidism, sensorineural deafness, and renal anomalies syndrome (Barakat syndrome)	Sensorineural hearing loss	Congenital anomalies of the kidney and urinary tract (cystic, dysplastic, hypoplastic or aplastic kidneys, pelvicalyceal deformity, vesicoureteral reflux)	*GATA3*
Kallmann syndrome	Hearing loss	Renal agenesis	*ANOS1, CHD7, FGF8, FGFR1, PROK2, PROKR2*
Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS)	Hearing loss	Fanconi syndrome; focal segmental glomerulosclerosis; kidney failure	mtDNA point mutations
MYH9-related disease	Sensorineural hearing loss	Hematuria; proteinuria; kidney failure; focal segmental glomerulosclerosis; irregular thinning and thickening of glomerular basement membrane with lamellated and basket-weave appearance	*MYH9*
Pendred syndrome	Sensorineural hearing loss; enlarged vestibular aqueduct	Acid–base disturbances	*SLC26A4*
Townes-Brocks syndrome	External ear anomalies; hearing loss	Dysplastic kidneys or agenesis; horseshoe kidney; multicystic kidney; posterior urethral valves; vesicoureteral reflux; kidney failure	*SALL1*
X-linked hypophosphatemia	Hearing loss	Hypophosphatemia; kidney stone	*PHEX*

MYH9-Related Disease: Cataracts and abnormal liver enzymes



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Cataracts (15% of patients)

- ***General Characteristics***
  - Cataracts typically onset at the mean age of 37 years, with most cases being bilateral and progressing over time
- ***Evaluation***
  - Ophthalmologic slit lamp examination

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Increase in liver enzymes (50% of patients)

- ***General characteristics***
  - Elevated liver enzyme levels usually remain stable over time
- ***Evaluation***
  - Measurement of serum concentration of aspartate aminotransferase and/or alanine aminotransferase

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MYH9-Related Disease: Management of thrombocytopenia and bleeding tendency

Treatment

- Local measures, transfusion of platelet concentrates, eltrombopag, antifibrinolytic drugs, desmopressin
- Oral contraceptives to prevent or control menorrhagia; regular dental care to prevent gum bleeding

Avoidance

- ***Agents***
  - Drugs that inhibit platelet function, such as nonsteroidal anti-inflammatory drugs, especially aspirin. Some antidepressants, antibiotics, and anesthetics.
  - Antithrombotic drugs (such as heparin or oral anticoagulants) should be prescribed with caution
- ***Circumstances***. Activities that associate high risk of trauma

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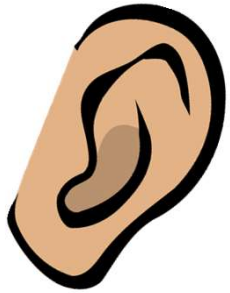
MYH9-Related Disease: Management of sensorineural hearing loss



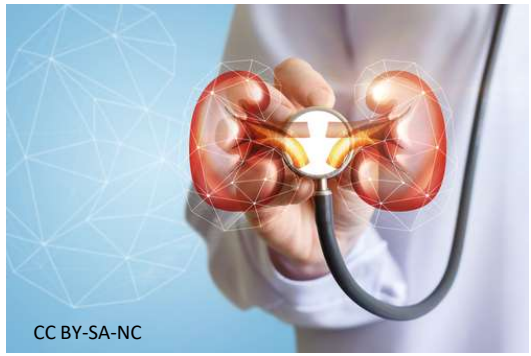
Treatment

- Hearing aids
- Cochlear implantation

Avoidance

- ***Agents***. Ototoxic drugs (aminoglycoside antibiotics, salicylates, loop diuretics)
- ***Circumstances***. Use ear devices (earplugs, headphones) to attenuate intense exposure to hazardous noise

MYH9-Related Disease: Management of nephropathy



Treatment

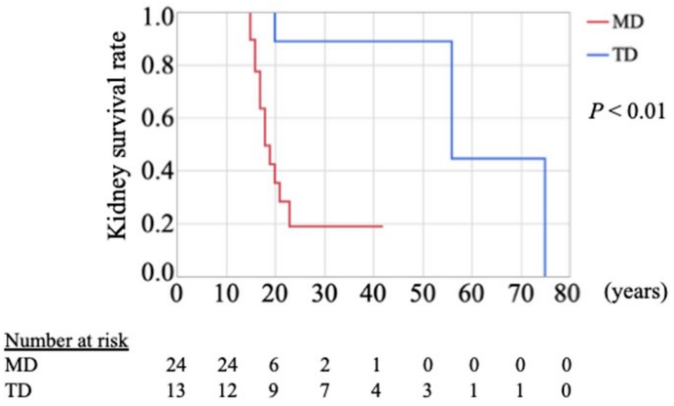
- Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers
- Dialysis, kidney transplantation

Avoidance

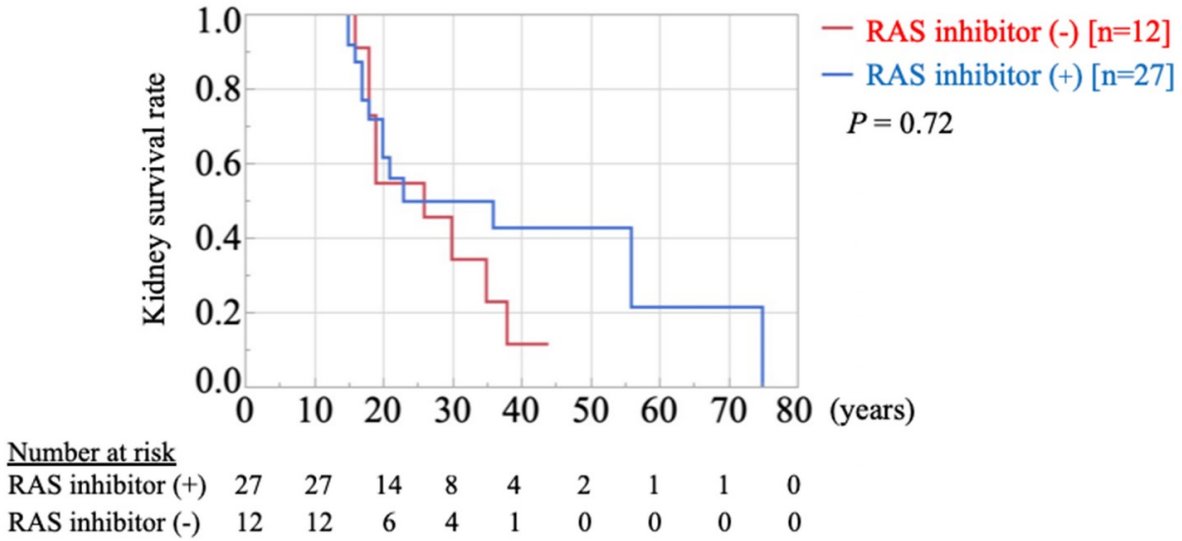
- ***Agents.*** Radiographic contrast agents, antibiotics, non-steroidal antiinflammatory drugs, diuretics

Kidney survival depending on the location of variant and specific treatment

Patients with variants affecting the Motor Domain have significantly worse kidney survival tan those with variants affecting the tail domain

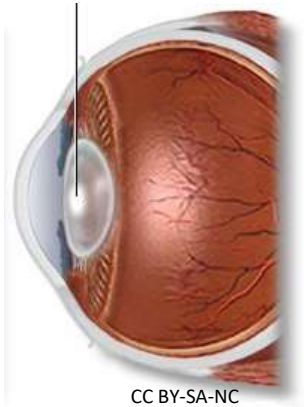


Kidney survival is similar between patients treated with and without renin angiotensin system inhibitors



Shirai Y, et al. Clin Exp Nephrol. 2024;28:40-49

MYH9-Related Disease: Management of cataracts and abnormal liver enzymes



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Treatment

- Cataract surgery
- No specific treatment for increased liver enzymes

Avoidance

- Cataracts: glucocorticoids
- Elevation of liver enzymes: potentially hepatotoxic drugs

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Recommended Surveillance for Individuals with *MYH9*-Related Disease

Thrombocytopenia and bleeding tendency	Neurosensorial hearing loss	Nephropathy	Cataracts	Abnormal liver enzymes
Clinical history and microscopic platelet count	Audiogram	Urinalysis	Ophthalmologic exam including slit lamp	Serum AST, ALT, and GGT
At least annually AND prior to hemostatic challenges	At least every 3 years AND as required in case of reported worsening of hearing function	Annually, OR every 6 months in genotypes with high risk of kidney damage	Every 3 years AND as required if reported symptoms suggestive for cataract	Every 3 years

Savoia A, Pecci A. MYH9-Related Disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2689/

MYH9-RD: Genetic counseling

MYH9-related disease (MYH9-RD) is inherited in an autosomal dominant manner

Approximately 65% of probands diagnosed with *MYH9*-RD have an affected parent

- In this case, 50% of siblings (and offspring) can inherit the MYH9 pathogenic variant. Family members may have a different phenotype (within the spectrum of MYH9-RD) than the proband

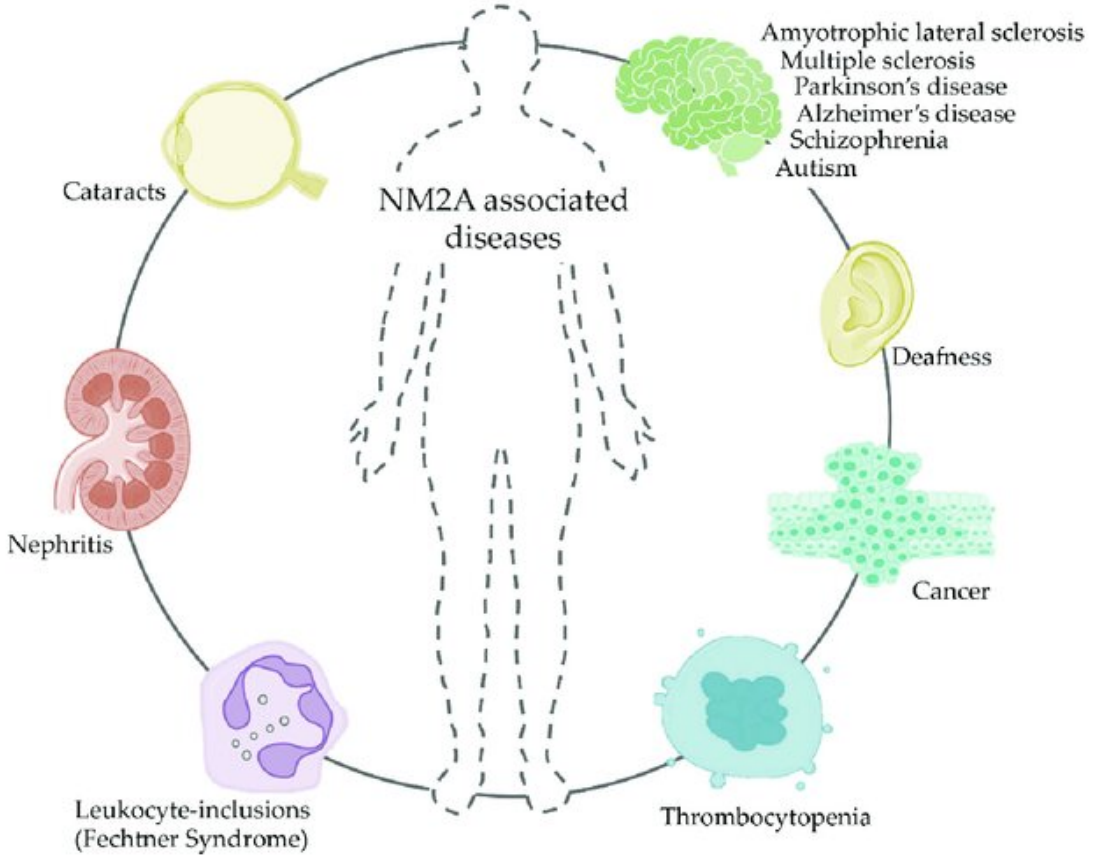
About 35% of probands represent simplex cases

- Most of these individuals have the disorder as the result of a *de novo* pathogenic variant
- In the minority of cases the proband may have inherited the pathogenic variant from a parent with germline (or somatic and germline) mosaicism

It is appropriate to offer genetic counseling to young adults who are affected or at risk

- Once the *MYH9* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible

Human disorders associated with mutations in MYH9, NM2A expression and/or activity defects



Brito C, Sousa S. Cells. 2020;9:1590

Thank you

Grupo Español de Alteraciones Plaquetarias Congénitas

Murcia Platelet Group
Dra. Marisa Lozano, Dr. José Rivera,

https://www.isth.org/events/EventDetails.aspx?id=1800387&group=
https://seth.es/advanced-course-platelet-research/

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